Childhood Diabetes in China

Enormous variation by place and ethnic group

ZE YANG, MD, PHD
KEAN WANG, MD
TIANLIN LI, MD
WEI SUN, MD
YURUI LI, MS
YUE-FANG CHANG, PHD
JANICE S. DORMAN, PHD
RONALD E. LAPORTE, PHD

OBJECTIVE— To investigate the incidence rate of IDDM in China.

RESEARCH DESIGN AND METHODS— The Chinese IDDM registry was established in 1991 as part of the World Health Organization's Multinational Project for Childhood Diabetes (DiaMond) project. Twenty-two centers were developed to monitor the incidence of IDDM in children <15 years of age. The population under investigation includes >20 million individuals, representing ~7% of the children in China. Capture-recapture methods were used to estimate the ascertainment.

RESULTS— The overall ascertainment-corrected IDDM incidence rate in China was 0.51 per 100,000, the lowest rate ever reported. There was a 12-fold geographic variation (0.13–1.61 per 100,000). In general, the incidence rate was higher in the north and the east. There was a sixfold difference among ethnic groups (highest: Mongol group, 1.82 per 100,000; lowest: Zhuang group, 0.32 per 100,000).

CONCLUSIONS— China has an extremely low overall IDDM incidence rate. China also has the greatest geographic and ethnic variation seen for any country.

IDDM is one of the most important chronic diseases of children worldwide. During the past few years, considerable information has been gained on the geographic and temporal patterns of IDDM in Europe and America (1,2). However, little is known about incidence in the Asian countries, especially mainland China. China may be one of the best countries to study the etiology of IDDM, as China has one-fourth of the world's population, 56 ethnic groups spread over 9.6 million square kilometers, and remarkably different climates, diets, and patterns of infectious diseases. Preliminary data in Shanghai and Tianjin suggested that China could have the lowest IDDM incidence in the world (3,4).

To evaluate the IDDM incidence rate in China, a collaborative registry network was set up in 1991 based on the World Health Organization's Multinational Project for Childhood Diabetes (DiaMond project) (5). The objectives of the current study were to map the incidence of IDDM in the largest registry in the world (6).

RESEARCH DESIGN AND METHODS

Registries

The Chinese IDDM registry was established in 1991 as part of the WHO DiaMond Project. There are 22 centers in this registry (Fig. 1), which cover 0.4 million km^2. In total, according to the 1990 Chinese census data, 20,654,990 children <15 years of age were monitored, which represents ~7% of the children in China. The centers cover seven major ethnic groups of China: Han, Man, Mongol, Hui, Zhuang, Uigur, and Korean. Han composes the majority, i.e., 95% of the children monitored in this study were Han. There were 233 physicians participating. There have been two WHO DiaMond training sessions in China, and each center has had a site visit at least once.

This study was primarily conducted from 1985 to 1994; however, it differed slightly from center to center. To obtain the IDDM cases that were diagnosed before 1991, a retrospective registration was applied by reviewing the records from the primary and secondary sources (described in the next section). Descriptive data on the populations for the study period are presented in Table 1. The definition of an IDDM case was according to WHO DiaMond criteria (5), i.e., individuals were diagnosed by a physician, placed on daily insulin injections before the 15th birthday, residents in the defined areas of registration at the time of the first insulin administration, and age 0–14 years at the time of diagnosis.

Case ascertainment

Data were obtained from at least two independent sources. As a primary source, cases were identified from the medical records in the hospital by a member of the local center. Students' physical examination records from the school health program were used by the majority of centers as their secondary source. Other sources included the records of approval of the birth of a second child from the Family Planning Committee, the insurance companies' payment voucher for the hospitalization of an IDDM child, local educational authority records excusing an IDDM child from taking the physical education examination, Child-Woman Care

Figure 1—*IDDM registration centers in China.*

From the Chinese Academy of Preventive Medicine (Z.Y., K.W., T.L., W.S., Y.L.), Diabetes and Other Non-Communicable Disease Research Center, Beijing, China; and the Department of Epidemiology (Y.-F.C., J.S.D., R.E.L.), Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address correspondence and reprint requests to Ze Yang, MD, PhD, Institute of Geriatrics, Ministry of Public Health, 1 Dahua Road, Dongdan Beijing 100730, PR China.

Received for publication 6 August 1997 and accepted in revised form 3 December 1997.

Abbreviations: DiaMond, Multinational Project for Childhood Diabetes; WHO, World Health Organization.

Table 1—*Target population and study period in 22 areas in China*

Areas	Registry period	Total population	Cases	Han population	Other ethnic population	Cases	Other ethnic groups
Beijing	1988–1994	2,181,046	136	2,098,166			
Changchun	1985–1994	461,858	35	439,810			
Changsha	1989–1994	1,357,437	19	1,354,874			
Dalian	1989–1994	450,780	27	419,850	25,437	1	Man
Guilin	1989–1994	334,448	9	330,187	59,958	5	Hui
Harbin	1989–1994	1,294,154	41	1,294,154			
Hainan	1989–1994	2,169,229	20	2,169,229			
Huhehot	1988–1994	340,341	21	340,341	31,435	4	Mongol
Jilin	1989–1994	745,048	25	745,048			
Jinan	1989–1994	1,196,929	27	1,196,929			
Lanzhou	1989–1994	597,886	11	597,886			
Nanjing	1990–1994	1,227,559	19	1,227,559			
Nanning	1989–1994	748,012	15	224,391	523,597	10	Zhuang
Qiqihar	1991–1994	50,988	4	50,988			
Shanghai	1989–1993	1,413,398	58	1,388,824			
Shenyang	1988–1994	1,249,343	34	1,121,629	19,103	2	Korean
Tieling	1988–1994	642,647	11	421,805			
Wulumuqi	1990–1994	264,875	9	163,759	11,713	1	Uigur
Wuhan	1989–1994	1,504,790	28	1,504,790			
Zhengzhou	1989–1994	431,479	12	431,479			
Zigong	1989–1994	1,133,774	26	1,133,774			
Zunyi	1989–1992	858,969	5	858,969			
Aggregate	1985–1994	20,654,990	592	1,9514,441	671,243	23	

All demographic data are from the 1990 census in China.

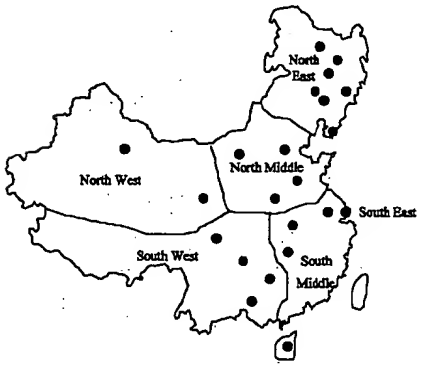

Figure 2—*Geographic regions in China.*

Network records, and the records from anti-epidemic stations. To ensure the quality of the data, 10% of the cases were randomly selected for reexamination at each center.

Statistical analysis

The two-sample capture-recapture method was used to evaluate the degree of ascertainment and generate the ascertainment-corrected incidence rate (7–9). The most important assumption of the two-sample capture-recapture method is that the primary and secondary sources are independent. The sources used in the current study are believed to be independent from each other because they have completely different paths to the identification of the IDDM children. This is now the standard procedure for IDDM registry (5).

To account for the different periods of study at each center, the population at risk was estimated by multiplying the 1990 Chinese census data by each center's follow-up time. The ascertainment-corrected IDDM incidence rate was calculated as the estimated number of IDDM cases from the capture-recapture method divided by the population at risk.

To further study the geographic variation in the IDDM incidence rates, the cen-

Table 2—*IDDM cases and the ascertainment-corrected incidence rates in six regions of China*

Region	Centers	Population	Person-years	Observed cases	Estimated cases	Estimated rate/ 100,000 (95% CI)
Northeast	7	4,894,818	33,006,354	177	180	0.55 (0.53–0.56)
North middle	4	4,149,795	27,420,157	196	218	0.79 (0.73–0.85)
Northwest	2	862,761	4,911,691	20	20	0.41 (0.39–0.43)
Southeast	2	2,640,947	13,204,785	77	90	0.68 (0.57–0.80)
South middle	3	5,031,456	30,188,736	67	70	0.23 (0.21–0.26)
Southwest	4	3,075,203	16,733,280	55	60	0.36 (0.31–0.41)

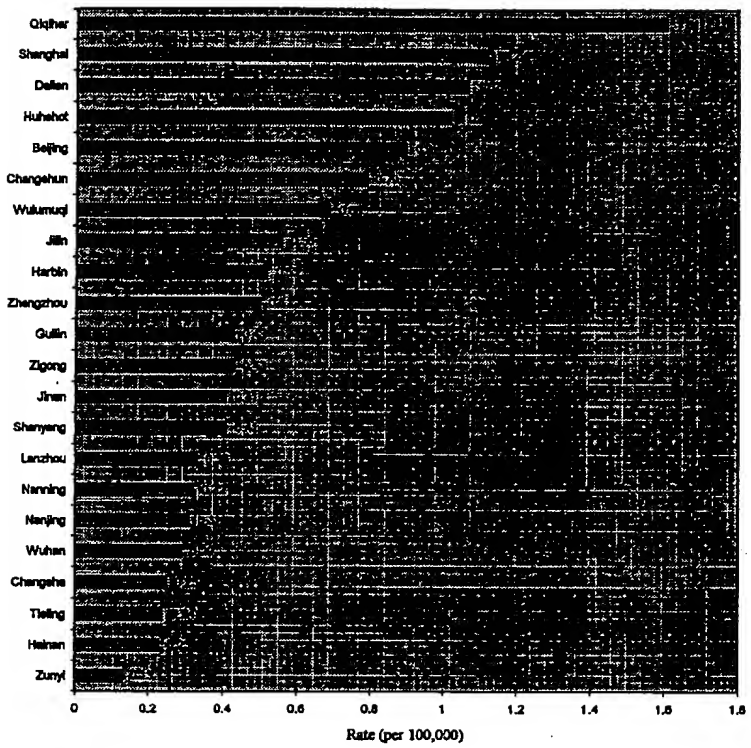

Figure 3—*IDDM ascertainment-corrected incidence rates in 22 centers in China.*

ters were grouped according to six major geographic regions (Fig. 2), different degrees of latitude, and locations south and north of the Yangtze River. The number of centers and the size of the population monitored in each region are presented in Table 2.

The incidence rate was age adjusted using indirect standardization method. The 1990 population of China was used as the standard population.

RESULTS

Overall incidence

During this investigation period, 592 IDDM cases were identified from 22 centers. Of these cases, 566 were identified in the hospitals, 256 were found from a secondary source, and 230 were in both sources. The crude incidence rate was 0.48 per 100,000 with a 95% CI of 0.38–0.56 per 100,000. Based on the capture-recapture method, it was estimated that there were 630 IDDM cases (95% CI 609–651), with an ascertainment-corrected incidence rate of 0.51 per 100,000 (95% CI 0.49–0.52 per 100,000). The overall ascertainment rate was 94% (95% CI 90.9–97.2). Sex-specific incidence rates were 0.47 per 100,000 for boys and 0.59 per 100,000 for girls. The age-specific incidence rate was lowest for the 0–4 years age-group and highest for the 10–14 years age-group. The overall age-adjusted IDDM incidence rate was 0.5 per 100,000 (95% CI 0.41–0.60 per 100,000).

Geographic variation

The IDDM ascertainment-corrected incidence rates for the 22 centers are presented in Fig. 3. There was a 12-fold difference between the highest (1.61 per 100,000 in Qiqihar) and the lowest rates (0.13 per 100,000 in Zunyi). Among the six geographic regions, the north middle region had the highest incidence rate (0.79 per 100,000) and the south middle region had the lowest rate (0.23 per 100,000) (Table 2). Centers north of Yangtze River had a significantly higher rate than those in the southern area (0.69 vs.0.34 per 100,000, $P < 0.001$). The incidence rate also increased with northern latitude (Fig. 4).

Ethnic variation

The numbers of IDDM cases in different ethnic groups are listed in the last column of Table 1, and the incidence rates for these groups are given in Table 3. There was a sixfold difference between the highest (Mongol: 1.82 per 100,000) and the lowest (Zhuang: 0.32 per 100,000) ethnic groups. However, it should be noted that the confidence intervals for the incidence rates were wide because of the small subgroup population size.

CONCLUSIONS— The Chinese IDDM registration system is the largest ever constructed for IDDM (6). The incidence of IDDM for children <15 years old in China is the lowest ever reported in the world (10). In the U.S., it has been estimated that 9,750 cases of IDDM develop each year in

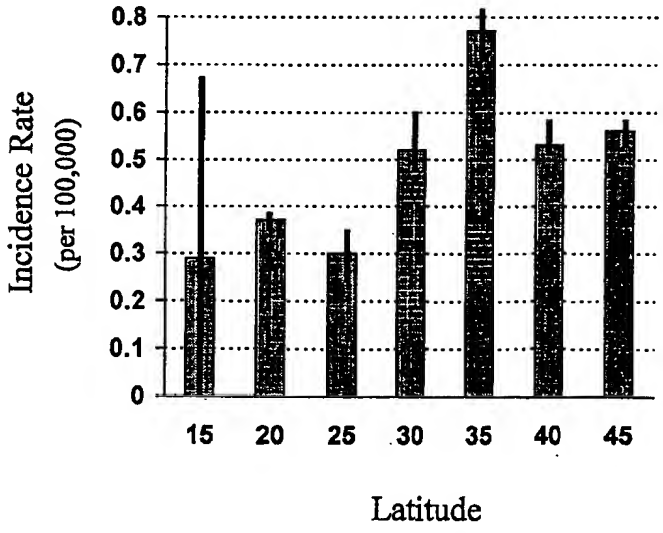

Figure 4—*IDDM incidence rate in China by latitude with 95% CI.*

Table 3—*IDDM incidence rates among seven major ethnic groups in China*

Ethnicity	Population	Person-years	Observed cases	Rate/100,000 (95% CI)
Han	19,514,441	118,227,795	569	0.48 (0.44–0.52)
Man	25,437	152,622	1	0.66 (0.00–3.94)
Hui	59,958	359,748	5	1.39 (0.56–3.34)
Mongol	31,435	220,045	4	1.82 (0.45–4.54)
Zhuang	523,597	3,141,582	10	0.32 (0.16–0.57)
Korea	19,103	133,721	2	1.50 (0.00–5.23)
Uigur	11,713	58,565	1	1.71 (0.00–10.26)

children 0–14 years old (11). If the U.S. incidence rates were the same as those in China, only 363 cases would have occurred. The global variation seen in IDDM now is truly remarkable: a child in Finland is 406 times more likely to develop diabetes than a child in Zunyi, China (12).

One might argue that the low incidence rates observed in China are simply a result of missing cases. However, the 22 centers were evenly distributed throughout China, and multiple sources were used to identify the cases. Furthermore, the health care at each center was also virtually identical. Thus, it is unlikely that many IDDM patients were missed by all the sources. Very few children with diabetes die without having been diagnosed with IDDM. In the Chinese health care system, any condition sufficiently severe will be rapidly moved from the Red Cross station, which is the local health center, to the health care organization that provides secondary to tertiary care. School students are also examined by physicians on a yearly basis. Thus, the loss of cases due to mortality without diagnosis of diabetes would be rare. Also, the capture-recapture method allows the number of cases missed to be formally estimated and adjusted for.

Although China has the lowest overall IDDM incidence rate ever reported, the rates varied dramatically from center to center. The centers in the north had higher rates than those in the south, and those in the east had higher rates than those in the west. Overall, there was a 12-fold difference among the centers. This is larger than what has been observed in other studies, e.g., variation was fivefold for Caucasians in the U.K. and threefold among U.S. blacks, but no variation has been observed among the Japanese (11,13,14). This huge variation is very possible because of both the diversified genetic background in the Chinese population and the exposure to different environmental factors throughout the whole area. In China, different areas have very different eating habits and lifestyles. Each ethnic group also has a very different genetic background. Han, the major ethnic group, which is distributed all over China, constitutes more than 92% of the total population, whereas the minor ethnic groups making up the other 8% live in specific geographical areas. In the current study, the four groups with the highest IDDM incidence (Mongol, Uigur, Hui, and Korean) primarily live in the northern part of China. The group (Zhuang) with the lowest IDDM incidence rate resides in the southwestern area. Among these ethnic groups, Hui and Uigur are Caucasians. However, they still have much lower IDDM rates than do most of the Western countries. In general, the minority groups in the northern part of China have some degree of Caucasian or mixture of Caucasian and Mongolian genetic makeup. HLA gene frequency studies have also revealed that allelic differences exist not only among ethnic groups but also between the northern and southern Han populations of China (15–19). This may imply that although genetics is an important risk factor for IDDM, environmental factors also contribute, explaining part of the variation seen across these groups.

As attempts are made to further elucidate the causes of IDDM around the world, it will be extremely important to compare the risk obtained from this study to those in the U.S. Previous research has indicated that there is a fourfold increase in incidence in Hong Kong as well as Singapore and Taiwan. But what about differences in rates between Chinese children and U.S. Chinese children? We do not know, as there is no incidence data on Chinese-Americans. For this reason, further studies must be conducted, and would be clearly the next step of our research. By studying the differences in rates between U.S. Chinese children and Chinese children, other risk factors or roles of currently known risk factors may become better understood.

Acknowledgments— Coordination of the Chinese Child IDDM Epidemiology project was financially supported by National Institutes of Health Grant R01-DK46498.

Leaders of local study centers in WHO Chinese DiaMond task force were Beijing, Dr. C. Yan, Dr. G. Ni, Beijing Children Hospital, Beijing; Changchun, Dr. C. Li, Dr. Y. Deng, Bethiun Medical University, Changchun; Changsha, Dr. Z. Zhou, Hunan Medical University, Changsha; Dalian, Dr. Z. Sun, Dr. D. Liu, Urban Anti-Epidemic Station, Dalian; Guilin, Dr. X. Fang, Maternity and Child Care Hospital, Guilin; Harbin, Dr. B. Wang, Public Health College, Harbin Medical University, Harbin; Hainan, Dr. S. Fu, General Hospital of Hainan Province, Haikou; Huhehot, Dr. S. Zhao, Dr. Z. Gui, Dr. S. Pang, Dr. A. Liu, Urban Anti-Epidemic Station, Huhehot; Jilin (two regions), Dr. Y. Zhang, Institute of Occupational Medicine of Jilin Province, Changchun; Jinan, Dr. S. Chen, Dr. L. Fu, Shandong Province Qianfeshan Hospital, Jinan; Lanzhou, Dr. K. Yang, Dr. D. Wang, Lanzhou Medical College, Lanzhou; Nanjing, Dr. J. Shen, Dr. Y. Xu, Nanjing Medical University, Nanjing; Nanning, Dr. S. Wang, Dr. H. Yang, Dr. L. Yan, Province Anti-Epidemic Station, Nanning; Qiqihar, Dr. L. Wang, Qiqihar Medical College, Qiqihar; Shanghai, Dr. S. Shen, Dr. Y. Shen, Dr. H. Fu, Dr. J. Wang, Dr. H. Wang, Dr. T. Ye, Shanghai Medical University, Shanghai; Shenyang, Dr. Y. Liu, Urban Anti-Epidemic Station, Shenyang; Tieling, Dr. B. Yang, Liaoning Province Anti-Epidemic Station, Shenyang; Wulumuqi, Dr. K. Teng, Dr. L. Liu, Army General Hospital, Wulumuqi; Wuhan, Dr. L. Shi, Dr. Q. Zhang, Tongji Medical University, Wuhan; Zhengzhou, Dr. J. He, Dr. J. Jiang, Henan Province Anti-Epidemic Station, Zhengzhou; Zigong, Dr. X. Wu, Dr. D. Wang, Sichuan Province Anti-Epidemic Station, Chengdu; Zunyi, Dr. Y. Lei, Zunyi Regional Anti-Epidemic Station, Zunyi.

Members of the project management group were Dr. R. LaPorte, Dr. J. Dorman, Dr. K. Wang, Dr. T. Li, Dr. Z. Yang, Dr. N. Tajima, Dr. W. Sun.

Members of the consultant group were Dr. K. Wang, Dr. C. Zhou, Dr. Z. Chi, Dr. X. Chen, Dr. X. He, Dr. R. Qian, Dr. C. Yan, Dr. G. Jiang, Dr. F. He, Dr. Y. Li, Dr. S. Jin, Dr. N. Tajima, Dr. S. Baba, Dr. H. King.

Members of the project steering group were Dr. Z. Yang, Y. Wei, H. Chen, S. Jin, R. Qin.

WHO China DiaMond Group: Dr. Y. F. Chang, Dr. A. Sekikawa, Dr. N. Tajima.

Site visitors were Dr. Z. Yang, Dr. Z. Wu, Dr. T. Li, Dr. Y. Deng, Dr. R. LaPorte, Dr. J. Dorman.

References

1. Rewers M, LaPorte RE, King H, Tuomilehto J, for The Diabetes Epidemiology Research

International Study Group-DERI: Trends in the prevalence and incidence of diabetes: insulin-dependent diabetes mellitus in childhood. *World Health Stat*41:179–189, 1988
2. LaPorte R: Patterns of disease: diabetes mellitus and the rest. *BMJ*310:545–546, 1995
3. Hua F, Shui-xian S, Zhao-wen C, Jia-jun W, Ting-ting Y, LaPorte RE, Tajima N: Shanghai, China, has the lowest confirmed incidence of childhood diabetes in the world. *Diabetes Care*17:1206–1208,1994
4. Bao MZ, Wang JX, Dorman JS, Trucco M: HLA-DQB non-ASP-57allele and incidence of diabetes in China and USA (Letter). *Lancet*ii:497–498, 1989
5. WHO Multinational Project for Childhood Diabetes, Methods of Operation: 1991
6. Vaananen S, Kohtamaki K, Karvonen J, Tuomilehto J, for the DiaMond Research Group: Incidence of IDDM worldwide: preliminary analysis of the WHO DIAMOND incidence data. *Poster session at the 1997 International Diabetes Epidemiology Group Symposium*Savonlinna, Finland, July 1997
7. LaPorte RE, Barinas E, Chang YF, Libman I: Global epidemiology and public health in the 21st century: applications of new technology. *Ann Epidemiol*6:162–167, 1996
8. International Working Group for Disease Monitoring and Forecasting: Capture-recapture and multiple-record systems estimation. I. History and theoretical development. *Am J Epidl*42:1047–1058, 1995
9. International Working Group for Disease Monitoring and Forecasting: Capture-recapture and multiple-record systems estimation. II. Applications in human disease. *Am J Epidl*42:1059–1068, 1995
10. Karvonen M, Tuomilehto J, Libman I, LaPorte R: A review of the recent epidemiological data on the worldwide incidence of type I (insulin-dependent) diabetes mellitus: World Health Organization DIAMOND Project Group. *Diabetologia*36:883–892, 1993
11. LaPorte RE, Matsushima M, Chang YF: Prevalence and incidence of insulin-dependent diabetes. In *Diabetes in America*2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Washington, DC, U.S. Govt. Printing Office, 1995, p. 37–46 (NIH publ. no. 95-1468)
12. LaPorte RE, Tajima N, Akerblom HK, Berlin N, Brosseau J, Christy M, Drash AL, Fishbein H, Green A, Hamman R, Harris M, King H, Laron Z, Neil A: Geographic differences in the risk of insulin-dependent diabetes mellitus: the importance of registries. *Diabetes Care*8 (Suppl. 1):101–107, 1985
13. Tajima N, LaPorte RE: Incidence of IDDM outside Europe. *Pediatr Adoles Endocrinol* 21:1–11, 1991
14. Burden AC, Hearnshaw JR: Rising incidence of IDDM in Europe. *Diabetes Care* 6:334–336, 1989
15. Dorman JS, LaPorte RE, Stone RA, Trucco M: Worldwide differences in the incidence of type I diabetes mellitus are associated with amino acid variation at position 57 of the HLA-DQB chain. *Proc Natl Acad Sci USA* 38:24–30, 1990
16. Gao X, Sun YP, An J, Fenandez-Vina M, Qou J, Lin L, Stastny P: DNA typing for HLA-DR and -DP alleles in a Chinese population using the polymerase chain reaction and oligonucleotide probes. *Tissue Antigens* 38:24–30, 1991
17. Wang FQ, Semana G, Fauchet R, Genetet B: HLA-DR and -DQ genotyping by PCR-SSO in Shanghai Chinese. *Tissue Antigens* 41:223–226, 1993
18. Diabetes Epidemiology Research International Group: Secular trend in incidence of childhood IDDM in 10 countries. *Diabetes* 39:858–864, 1990
19. Drash L, Cho N, Tajima N, Rewers M, LaPorte R: The epidemiology of diabetes in childhood with special reference to the Orient: implications for mechanism of beta cell damage. *Indian J Pediatr*56:S15–S32, 1989